Clinical Criteria

Subject:	Kymriah (tisagenlecleucel)		
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Table of Contents

Overview

This document addresses the use of Kymriah (tisagenlecleucel). Kymriah is a CD19-directed immunotherapy that is used to treat B-cell precursor acute lymphoblastic leukemia (ALL) and large B-cell lymphoma.

The FDA approved indications for Kymriah include individuals up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (also called acute lymphocytic leukemia) that is refractory or in second or later relapse, and for adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma, and DLBCL from follicular lymphoma.

Kymriah is a CD19-directed genetically-modified autologous T-cell immunotherapy, also known as chimeric antigen receptor (CAR) T-cell therapy. CAR T-cells are made by first collecting T-cells from the patient. The cells are then sent to a laboratory where they are genetically engineered to produce chimeric antigen receptors. The modified T-cells, now known as CAR T-cells, have the ability to better recognize an antigen (the CD19 protein) on targeted tumor cells. After the CAR T-cells have multiplied in the laboratory, they are then infused back into the patient. The modified CAR T-cells help the body's immune system better target and treat the tumor cells.

Kymriah has a black box warning for cytokine release syndrome (CRS), and should not be administered in patients with active infection or inflammatory disorders due to risk of life-threatening reactions and death. Severe or life-threatening CRS should be treated with tocilizumab with or without corticosteroids. Kymriah also has black box warning for causing neurological toxicities, which could also be severe and life-threatening. Monitoring for neurological events after administration is recommended. Due to these black box warnings, Kymriah is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.

Definitions and Measures

Allogeneic cells: Harvested from a histocompatible donor.

Autologous cells: Harvested from the individual's own cells.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

Chemotherapy: The medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Chimerism: Cell populations derived from different individuals; may be mixed or complete.

Complete Response (CR): The disappearance of all signs of cancer as a result of treatment; also called complete remission; does not indicate the cancer has been cured.

Cytotoxic: Treatment that is destructive to cells, preventing their reproduction or growth.

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ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- **0 = Fully active, able to carry on all pre-disease performance without restriction**
- **1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work**
- **2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
- **3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours**
- **4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair**
- **5 = Dead**

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow.

Karnofsky Performance Status: A scale and criteria used by doctors and researchers to assess an individual's prognosis, measure changes in their function and abilities, and determine their ability to tolerate therapies. The lower the score (from 0-100), the worse the likelihood of survival.

- **100 = Normal, no complaints**
- **90 = Able to carry on normal activities**
- **80 = Normal activity with effort**
- **70 = Care for self. Unable to carry on normal activity or to do active work**
- **60 = Requires occasional assistance, but able to care for most of his needs**
- **50 = Requires considerable assistance and frequent medical care**
- **40 = Disabled. Requires special care and assistance**
- **30 = Severely disabled. Hospitalization indicated though death nonimminent**
- **20 = Very sick. Hospitalization necessary. Active supportive treatment necessary**
- **10 = Moribund**
- **0 = Dead**

Lansky Score: A measure of the individuals overall physical health, judged by their level of activity; the score uses the following scale (generally reserved for individuals less than 16 years of age):

- **100 Fully active, normal**
- **90 Minor restrictions in physically strenuous activity**
- **80 Active, but tires more quickly**
- **70 Both greater restriction of and less time spent in play activity**
- **60 Up and around, but minimal active play; keeps busy with quieter activities**
- **50 Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities**
- **40 Mostly in bed; participates in quiet activities**
- **30 In bed; needs assistance even for quiet play**
- **20 Often sleeping; play entirely limited to very passive activities**
- **10 No play; does not get out of bed**
- **0 Unresponsive**

Line of Therapy:

- **First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.**
- **Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.**
- **Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.**

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

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Tyrosine kinase inhibitor: Type of drug which works by blocking several enzymes that promote cell growth, which has been found to be an effective approach to treat a variety of cancers. Examples include imatinib (Gleevec), dasatinib (Tasigna), nilotinib (Sprycel), bosutinib (Bosulif), and ponatinib (Iclusig).

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Kymriah (tisagenlecleucel)

Requests for Kymriah (tisagenlecleucel) for B-cell acute lymphoblastic leukemia may be approved if the following criteria are met:

I. Individual is 25 years of age or younger; AND
II. Individual has diagnosis of B-cell acute lymphoblastic leukemia; AND
III. Individual has confirmed CD19 tumor expression; AND
IV. Individual has relapsed or refractory disease defined by any of the following (NCT02228096):
    A. Second or later bone marrow relapse; OR
    B. Bone marrow relapse after allogeneic stem cell transplant; OR
    C. Primary refractory disease defined as failure to achieve complete response after two cycles of standard chemotherapy; OR
    D. Chemo-refractory after relapse defined as failure to achieve complete response after 1 cycle of standard chemotherapy for relapse leukemia; AND
V. If individual has Philadelphia chromosome positive (Ph+) ALL, confirmation of trial and inadequate response or intolerance to at least two tyrosine kinase inhibitor (TKI) therapies, or TKI therapy is contraindicated (NCCN 2A, NCT02228096); AND
VI. Individual has a Karnofsky or Lansky performance score of greater than or equal to 50%; AND
VII. Individual is using as a one-time, single administration treatment.

Kymriah (tisagenlecleucel) for B-cell acute lymphoblastic leukemia may not be approved for the following (Label, NCT02228096):

I. Using in combination with other chemotherapy agents (not including the use of lymphodepleting chemotherapy as labeled prior to Kymriah infusion); OR
II. Active central nervous system (CNS) 3 leukemia (CNS-3) found in cerebral spinal fluid (CSF), defined as white blood cell (WBC) count greater than or equal to 5 WBC/mcL with presence of lymphoblasts (NCCN); OR
III. Other forms of active CNS-3 leukemia with CSF involvement, such as CNS parenchymal or ocular disease, cranial nerve involvement, or significant leptomeningeal disease; OR
IV. Any acute or ongoing neurologic toxicity greater than Grade 1 as defined by the National Cancer Institute (NCI CTCAE v.5), not including history of controlled seizures or fixed neurologic deficits that have been stable/improving over the past three months; OR
V. Diagnosis of Burkitt's lymphoma/leukemia; OR
VI. History of chimeric antigen receptor therapy or other genetically modified T-cell therapy, including, but not limited to, previous administration of Kymriah or Yescarta (axicabtagene ciloleucel); OR
VII. Active or latent hepatitis B, active hepatitis C, human immunodeficiency virus (HIV) positive, or other active, uncontrolled infection; OR
VIII. Active neurological autoimmune or inflammatory disorders (for example, Guillain Barre Syndrome, Amyotrophic Lateral Sclerosis) (Label, NCT02445248); OR
IX. When the above criteria are not met, and for all other indications.

Requests for Kymriah (tisagenlecleucel) for large B-cell lymphoma may be approved if the following criteria are met:

I. Individual is 18 years of age or older; AND
II. Individual has a histologically confirmed diagnosis of one of the following:
    A. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; OR
    B. High-grade B-cell lymphoma; OR
    C. DLBCL from follicular lymphoma; AND
III. Relapsed or refractory disease, defined as progression after two or more lines of systemic therapy (which may or may not include therapy supported by autologous stem cell transplant), including all of the following:
    A. An anthracycline-containing chemotherapy regimen; AND
    B. Rituximab; AND
IV. Individual has adequate bone marrow reserve without transfusion defined by *all* of the following:
    A. Absolute neutrophil count (ANC) ≥ 1000 cells/uL; AND
    B. Absolute lymphocyte count (ALC) > 300 cells/uL; AND
    C. Platelet count ≥ 50,000 cells/uL; AND

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D. Hemoglobin > 8.0 g/dl; AND

V. Individual has a current ECOG performance status of 0-1; AND

VI. Individual is using as a one-time, single administration treatment.

Kymriah (tisagenlecleucel) for large B-cell lymphoma may not be approved for the following (Label, NCT02445248):

I. Diagnosis of primary central nervous system lymphoma; OR

II. Using in combination with other chemotherapy agents (not including the use of lymphodepleting chemotherapy as labeled prior to Kymriah infusion); OR

III. Active central nervous system (CNS) involvement by malignancy; OR

IV. Diagnosis of Burkitt's lymphoma/leukemia (NCT02228096); OR

V. History of allogeneic hematopoietic stem cell transplant, chimeric antigen receptor therapy or other genetically modified T-cell therapy, including, but not limited to, previous administration of Kymriah or Yescarta (axicabtagene ciloleucel); OR

VI. Active or latent hepatitis B, active hepatitis C, human immunodeficiency virus (HIV) positive, or other active, uncontrolled infection; OR

VII. Active neurological autoimmune or inflammatory disorders (for example, Guillain Barre Syndrome, Amyotrophic Lateral Sclerosis); OR

VIII. When the above criteria are not met, and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT	
0537T	Chimeric antigen receptor T-cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day [for Kymriah]
0538T	Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage) [for Kymriah]
0539T	Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration [for Kymriah]
0540T	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous [for Kymriah]
HCPCS	
Q2042	Tisagenlecleucel, up to 600 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose [Kymriah]
ICD-10 Procedure	
XW033C3	Introduction of engineered autologous chimeric antigen receptor T-cell immunotherapy into peripheral vein, percutaneous approach, new technology group 3 [when specified as Kymriah]
XW043C3	Introduction of engineered autologous chimeric antigen receptor T-cell immunotherapy into central vein, percutaneous approach, new technology group 3 [when specified as Kymriah]
ICD-10 Diagnosis	
C82.00-C82.99	Follicular lymphoma
C83.30-C83.39	Diffuse large B-cell lymphoma
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C91.00-C91.02	Acute lymphoblastic leukemia (ALL)
Z51.12	Encounter for antineoplastic immunotherapy

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Document History

Revised: 11/15/2019
Document History:

- **11/15/2019 – Annual Review, Coding reviewed : No Changes**
  - **Initial review of Kymriah (tisagenlecleucel) from medical policy MED.00124.**
    - **Add definition of primary refractory disease and chemo-refractory to ALL criteria.**
    - **Update ALL criteria to add trial and failure of two TKI therapies if disease is Philadelphia chromosome positive.**
    - **Update ALL criteria to remove ECOG performance status.**
    - **Remove overall non-approvable section for Kymriah, and separate into two non-approvable sections for ALL and DLBCL indications.**
    - **Clarify non-approvable ALL and DLBCL criteria for use with other chemotherapy agents.**
    - **Add specific non-approvable criteria for ALL regarding CNS disease severity per clinical trials.**
    - **Add diagnosis of Burkitt's lymphoma/leukemia to non-approvable ALL and DLBCL criteria.**
    - **Remove history of allogeneic stem cell transplant from ALL non-approvable criteria.**
    - **Clarify previous use of CAR-T drugs to ALL and DLBCL non-approvable criteria.**
    - **Add diagnosis of active neurological autoimmune or inflammatory disorders to ALL and DLBCL non-approvable criteria.**
    - **Remove history or presence of any central nervous system disease from ALL and DLBCL non-approvable criteria.**
    - **Clarified history of prior therapies in DLBCL criteria.**
    - **Add diagnosis of primary CNS lymphoma to DLBCL non-approvable criteria.**
    - **Add diagnosis of active CNS involvement by malignancy to non-approvable DLBCL criteria.**

References

1. **Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2019. URL: http://www.clinicalpharmacology.com. Updated periodically.**
2. **Common Terminology Criteria for Adverse Events (CTCAE), V5.0. Revised November 2017. National Institutes of Health, National Cancer Institute (NCI). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed September 25, 2019.**
3. **DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: September 25, 2019.**
4. **DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.**
5. **Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2019; Updated periodically.**
6. **NCCN Clinical Practice Guidelines in Oncology™. © 2019 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on September 25, 2019.**
   a. **Acute Lymphoblastic Leukemia. V2.2019. Revised May 15, 2019.**
   b. **B-Cell Lymphomas. V5.2019. Revised September 23, 2019.**
7. **NCT02228096. ClinicalTrials.gov. U.S National Library of Medicine, National Institutes of Health website. Available at https://clinicaltrials.gov/ct2/show/NCT02228096?term=nct02228096&rank=1. Accessed on September 25, 2019.**
8. **NCT02445248. ClinicalTrials.gov. U.S National Library of Medicine, National Institutes of Health website. Available at https://clinicaltrials.gov/ct2/show/NCT02445248?term=nct02445248&rank=1. Accessed on September 25, 2019.**

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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